REMARKS

I. Status of the Claims

Claims 1-48 remaining pending in this application. Claims 7, 8, 11-26, and 28-48, have been withdrawn from consideration. Claims 1-6, 9, 10, and 27, have been rejected.

II. Summary of the present invention

Applicants' surprising discovery is that a concentration of glycyrrhizin that is too low to be therapeutically effective actually enhances the antibiotic activity of a compound with which it is admixed. Since the inventive amount of glycyrrhizin is found to boost the activity of another antibiotic, much *less* of that antibiotic is needed to accomplish a desirable antibiotic effect. Furthermore, by adminstering less of an antibiotic, the incidence of any side effect that is associated with that antibiotic can be reduced. Moreover, since the concentration of glycyrrhizin has no antibiotic activity, it is highly unlikely that a pathogenic organism will develop resistance against it. Thus, the presently claimed invention captures a bioenhancing glycyrrhizin composition, wherein the glycyrrhizin has no antibiotic activity of its own.

III. Rejection of the Claims Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claim 6 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Examiner, since the concentration of glycyrrhizin can be up to 50% by weight of the anti-bacterial compounds "it is unclear how [glycyrrhizin] can be present in such as high concentration [sic] and ***not*** be pharmaceutically effective" (emphasis added). Office Action at page 2. The Examiner states that "this limitation seems in conflict with the limitation in claim 1 that states that the glycyrrhizin component cannot be present in a pharmaceutically effective amount." Office Action at page 2.

Applicants disagree with the Examiner's interpretation of the present claims and traverse the rejection. Claim 1 of the present invention requires the

Glycyrrhiza glabra extract or compound to be "insufficient by itself to be a therapeutically effective nutraceutical, antibiotic, anti-infective agent or anti-cancer agent," but that it ***is*** "effective as a bio-enhancer and bioavailability facilitator." In other words, present claim 1 prevents the use of a *Glycyrrhiza glabra* extract or compound at amounts that confer a therapeutic effectiveness upon the extract or compound itself. That extract or compound can be glycyrrhizin or glycyrrhizic acid, as recited in claim 3.

(A) *The prescribed range of glycyrrhizin concentration reflects the ratio of glycyrrhizin to an admixed antibiotic*

The concentration range of glycyrrhizin recited in claim 6, *i.e.*, 0.05% to 50%, reflects a ratio of **glycyrrhizin to an antibiotic**. That range does **not** prescribe an amount of glycyrrhizin that is to be administered to an individual. Claim 6 simply defines how much of glycyrrhizin must be admixed with the desired antibiotic, for the glycyrrhizin to be therapeutically ineffective by itself. Hence, claim 6 requires the glycyrrhizin to be "0.05 to 50% **of the weight of the anti-bacterial compounds**." Explicit support for such a range and concept can be found at page 6 of the present specification. Thus, one may use any amount of glycyrrhizin within the prescribed range, so long as the resultant amount is not therapeutically effective in and of itself. Accordingly, if a claimed composition comprised 100 μg/ml of an antibacterial agent, then one could select to add 0.05% of glycyrrhizin to the antibacterial agent, *i.e.*, to produce a glycyrrhizin concentration of 0.05 μg/ml. As Applicants have demonstrated in the present application, not even 1.0 μg/ml of glycyrrhizin alone had any therapeutic effect on killing, for instance, *Candida albicans*, as evidenced by the zero "zone of inhibition" in a disc diffusion assay. See, Table 4 at page 16 of the specification.

(B) *A concentration of glycyrrhizin that is 0.05% to 50% by weight of the antibiotic to which it is admixed, boosts that antibiotic's activity*

Moreover, Applicants have shown experimentally that a concentration of glycyrrhizin that is 0.05% to 50% by weight of the antibiotic to which it is admixed, boosts that antibiotic's activity. See, for instance, Table 1, at page 14 of the specification. There, Applicants show that the ratio of glycyrrhizin to any one of the tested antibiotics, *e.g.*, rifampicin, nalidixic acid, tetracycline, or ampicilin, ranges from 0.5% (1.0 μg of glycyrrhizin to 20 μg/ml of rifampicin) to 50% (1.0 μg of glycyrrhizin to 2.0 μg/ml of tetracycline). Yet, those amounts enhance the effectiveness of those antibiotics. When added to a therapeutically ineffective amount of glycyrrhizin, the antibiotic activity of a 20 μg/ml dose of rifampicin increased by 14-fold. Similarly, the ability of 2.0 μg/ml of tetracycline to kill cells was essentially doubled when 50% of glycyrrhizin was added to it.

Accordingly, claim 6 does not require that a ***composition*** to comprise 0.05% to 50% by weight of glycyrrhizin. Rather, claim 6 necessitates a **ratio of glycyrrhizin to the antibacterial agent** ***within*** the composition to be in the range of 0.05% to 50%.

(C) *The present claims require a prescribed range but use a concentration within that range that ensures the glycyrrhizin is not therapeutically effective.*

Furthermore, not only does claim 6 specify a certain range of amounts of glycyrrhizin, it also stipulates that the glycyrrhizin must not be in an amount that is therapeutically effective. Thus, there is no conflict between claim 6 and claim 1, as suggested by the Examiner. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

IV Rejection of the Claims Under 35 U.S.C. § 102(b)

Claims 1-5 and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,939,050. The Examiner states that "applicant's [sic] specification defines a non-therapeutically effective amount of Glycyrrhiza glabra extracts to be either 1 ug/ml, 4ug/ml, or 25 ug/ml (see pages 14, 16, and 19). US '050 teaches adding the Glycyrrhiza extracts in these amounts (see column 11, Table 6). Therefore, based on what applicants have defined as the proper amount of extract to add, US '050 is still considered to meet the limitations of the claims." Office Action at page 3.

(A) *The Examiner's characterization concentrations of the prior art and those of the present invention is wrong*

Applicants disagree with the Examiner's rationale for rejecting these claims and traverse the rejection. Firstly, the Examiner points to pages 14, 16, and 19, of the present specification to show that Applicants used glycyrrhizin at 1 μg/ml, 4 μg/ml, and 25 μg/ml. Applicants state at page 14 that "in all the experiments the glycyrrhizin concentration was kept at 1 μg/ml" unless otherwise denoted. The so-called "4 μg/ml" concentration that the Examiner notes at page 16, is in fact the concentration of *clotrimazole*, not glycyrrhizin. See, Table 4, which shows that a combination of 4 μg/***disc*** of clotrimazole and 1 μg/***disc*** of glycyrrhizin in a disc diffusion assay resulted in an enhanced zone of inhibition that was almost 1.6-fold better in irradicating *Candida albicans* than 4 μg/disc of clotrimazole alone. Applicants do not recite anywhere on page 16 that the concentration of glycyrrhizin is 4 μg/ml.

Similarly, the "25 ug/ml" that the Examiner states is disclosed at page 19 of the present specification in fact relates to the concentration of ***licorice***, not purified glycyrrhizin extract. Accordingly, the Examiner has misread and misinterpreted Applicants' disclosure.

(B) *Table 6 of the '050 patent teaches the use of antimicrobial-effective concentrations of a Glycyrrhiza glabra extract*

Furthermore, the Examiner points to Table 6 of the '050 patent as evidence of the prior art teaching "adding the *Glycyrrhiza* extract in these amounts." Yet, Table 6 of the '050 patent discloses no such parameters. Table 6 shows the effect of combining an *antimicrobial*-effective concentration of a *Glycyrrhiza glabra* extract with various other antimicrobial agents on certain bacteria. The '050 patent explains that "[V]arious combinations of the antimicrobial agents . . . were evaluated . . . to identify combinations of agents that will inhibit visible *in vitro* growth of microorganisms and evaluate the MIC [minimum inhibitory concentration] of the agents in the combination. In addition, the lowest concentration, e.g., (MIC), of ***each*** of the antimicrobial agents used in the two component combinations **that inhibited visible *in vitro* growth** of a particular microorganism was determined in accordance with the protocol set forth above," (emphasis added), column 9, line 62 to column 10 line 4.

The '050 patent does not teach the use of an antimicrobially-***ineffective*** amount of glycyrrhizin, rather it teaches the use of a *Glycyrrhiza glabra* extract in an amount sufficient to convey antimicrobial activity. Clearly, this alone teaches away from one of the most salient elements of the presently claimed invention, namely, the use of a concentration of glycyrrhizin that is therapeutically-ineffective by itself in inhibiting pathogen growth.

(C) *The '050 patent uses crude Glycyrrhiza glabra powdered extract, not glycyrrhizin as presently claimed*

Secondly, the '050 patent does not use glycyrrhizin. The '050 patent uses a crude *Glycyrrhiza glabra* extract. To wit: "'*Glycyrrhiza glabra* extract,' also known as licorice root extract, refers to the **crude powder extract** from *Glycyrrhiza glabra*," (emphasis added), column 4, lines 34-36. The crude powder extract contains various impurities and other compounds, like asparagin, glycyramarin, and starch in addition to glycyrrhizin, all of which may act

individually or synergistically with one another. For instance, it was recently demonstrated that the "potent antioxidants" of licorice root extract and "glabridin," which is an isoflavan purified from licorice root extract, could modulate the activities of several cytochrome P450 enzymes. See, the abstract of Kent *et al.*, Drug Metab. Dispos., 30(6):709-15, 2002, appended to this paper. Kent *et al.*, concludes that "P450 3A4, the major human drug metabolizing P450 enzyme, was inactivated by licorice root extract and by glabridin in a time-and concentration-dependent manner."

(D) *It is not possible to determine from the '050 patent the ratio of crude Glycyrrhiza glabra extract to "Agent B"*

Thirdly, Table 6 of the '050 patent recites only the minimum inhibitory concentration values for crude *Glycyrrhiza glabra* extract, it does relate the concentration of "Agent B." The latter concentrations were determined empirically according to the methodology of Example 1 at column 8. Accordingly, there is no way to ascertain from Table 6 alone whether the disclosed concentrations of *Gycyrrhiza glabra* extract meet the requirement of the present claims that it contains an amount of glycyrrhizin that is "0.05% to 50% of the weight" of the admixed Agent B, as recited in present claim 6.

In this respect, the '050 patent teaches away from this ratio of glycyrrhizin-to-anitbiotic. The '050 patent teaches that "the amount of the antimicrobial agent present is preferably selected so that once the composition is applied or delivered, the concentration of the antimicrobial agent is greater than the MIC of the antimicrobial agent with respect to a particular bacteria. Suitable amounts range from about 0.001 wt. % to about 5.0 wt. %, preferably about 0.01 wt. % to about 2.5 wt. % for each agent based on the **total weight of the composition** containing the agents" (emphasis added; column 7, lines 6-15).

(E) *The '050 patent produces an oral hygiene product that improves taste and reduces teeth-staining problems*

Fourth, the entire goal of the '050 patent is to produce an "oral hygiene product." The '050 patent states at the last paragraph of the Background of the Invention, that for oral preparations, chlorhexidine is the "standard against which other antimicrobial agents are measured," but that chlorhexidine "exhibits [an] ***undesirable taste and has the undesirable side effect of staining teeth***," (emphasis added; column 2, lines 48-52). Indeed, the '050 patent states that the "most preferred [antimicrobial agents] for combination with *Glycyrrhiza glabra* extract are antimicrobial agents selected from cedarwood oil, geraniol, juniper berries oil, *Rosmarinus officinalis* oil. The skilled artisan would understand, therefore, that there already existed a suitable antimicrobial agent for treating oral hygiene, but that the '050 patent sought to overcome the accompanying undesirable tastes and staining problems associated with that particular agent. Hence, the skilled artisan would appreciate that the fragrant oils admixed with the crude *Glycyrrhizin glabra* extract powder served to improve taste and staining problems, while simultaneously conveying antimicrobial activities.

In other words, the '050 patent does not seek to use glycyrrhizin as a non-antimicrobial agent for use in enhancing an antimicrobial. That is, the '050 patent does not disclose or contemplate the use of a crude *Glycyrrhizin glabra* extract at low enough concentrations to be ineffective as an antimicrobial but effective as a bioenhancer of, for instance, cedarwood oil.

(F) *The '050 patent does not teach each and every limitation of the presently claimed invention*

The sum of these distinctions leads to only one conclusion: that the '050 patent, in no uncertain terms, does not anticipate the presently claimed invention because the '050 patent does not teach each and every limitation of the rejected claims. Also, the '050 patent teaches away from Applicants'

invention. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

V. The present claims are not rend red obvious by the cited art

The Examiner rejects claims 1, 5, 6, 9, 10, and 27, as unpatentable over U.S. Patent No. 5,939,050, The Merck Index entries 2315, 6273, and 6617, and U.S. Patent No. 5,478,829, "for the reasons set forth on page 5 [of] the Office Action of ***December 15, 2002***" (emphasis added). Office Action at page 3. The Examiner explains that "since US '050 is still considered to teach the claimed invention, this rejection is still considered valid for the reasons of record." Office Action at page 3.

Applicants disagree with the Examiner's rationale for rejecting the claims as unpatentable, and traverse the rejection. At the outset, Applicants believe that the Office Action referred to should be the communication dated April 30, 2001. Applicants do not have in their records a copy of "December 15, 2002" Office Action. Applicants respectfully request that the Examiner confirm that the "December 15, 2002" date is incorrect, or ask that she forward a copy of that communication to the undersigned.

(A) *The Examiner acknowledges that the '050 patent teaches the use of G. glabra as an anti-bacterial agent*

Without more, Applicants overcome the Examiner's rejection by referring to her remarks at page 5 of the Office Action dated April 30, 2001. There, the Examiner stated that "US 050 teaches that *G. glabra* is an anti-bacterial agent," that the "Merck Index teaches that nalidixic acid, nofloxacin, and ciprofloxacin are anti-bacterial agents," and that "US '829 teaches that sparfloxacin is an anti-bacterial agent."

(B) *The present invention does not use glycyrrhizin as an antibacterial*

The Examiner relies on the Merck Index entries and the '829 patent to teach the specific quinolones and fluoro-quinolones recited in present claim 10. However, the Examiner clearly has misunderstood, or inappropriately dismisses the concept of, the present invention, despite Applicants' explicit remarks of June 18, 2002. The present invention, as detailed above, **does not use glycyrrhizin "as an anti-bacterial agent**." The present invention uses glycyrrhizin as a bioenhancer to enhance the activity of a separate antibacterial agent. That the Examiner acknowledges the '050 patent to teach the use of *Glycyrrhizia glabra* as an antibacterial agent, is alone sufficient to remove the '050 patent as a prior art reference. The present claims do not require the use of *Glycyrrhizia glabra* as an antibacterial agent, yet the Examiner maintains that the '050 patent anticipates the presently claimed invention. Instead, the '050 patent disclosure, and the Examiner's own summary of the '050 patent, **teach away** from the presently claimed elements.

(C) *The skilled artisan, from reading the combined prior art, would not optimize the concentration of crude G. glabra extract to abolish an antibacterial activity*

With regard to optimization, the Examiner admitted at page 6 of the April 30, 2001, Office Action, that "the references do not specifically teach adding the *G. glabra* extract in the amounts claimed by applicants." However, she countered that "it would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results." The Examiner's understanding of the present invention is wrong. Even if the '050 patent was applicable art, the artisan of ordinary skill would not expect the "optimized" crude *G. glabra* extract to be devoid of antibacterial activity, and furthermore, would not expect the crude *G. glabra* extract to **boost** the antibacterial activity of another ingredient with which it is formulated. Instead, the skilled artisan would optimize the concentration of *G. glabra* extract and expect it to confer an antimicrobially activity in conjunction

with the other antimicrobial ingredients in the composition. That is, the skilled artisan would have expected to obtain the direct ***opposite*** of what the presently claimed invention prescribes.

Accordingly, the claimed invention is not rendered obvious by the cited prior art, for the reasons set forth herein and in Section IV above, and therefore Applicants request that the Examiner withdraw this rejection.

VI. Conclusion

It is respectfully urged that upon entry of the proposed amendments, the examined claims are now in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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MARKED-UP VERSION

6. **The** [A] composition **of** [as claimed in] claim **2** [1], wherein the concentration of glycyrrhizin ranges from 0.05 to 50% of the weight of the anti-bacterial compounds.